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Jennifer K. Johnson, J.D.
Patent Department, ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102

EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,876	CONKLIN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33 and 35-53* is/are pending in the application.

4a) Of the above claim(s) *32,33 and 35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~1/31/05~~. 10/31/05 PTO
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 1/5/06 has been entered. Applicant has cancelled claims 1-31, 34, and added new claims 41-53. Claims 32-33, 35-40 are withdrawn. Claims 41-53 drawn to the elected invention of Group I will be examined as they pertain to the polynucleotide of SEQ ID NO:1. Oligonucleotides shown in SEQ ID NOs 15-17 and 19-20 will not be examined because they are not contained in the polynucleotide of SEQ ID NO:1 and would constitute distinct inventions. Oligonucleotides pertaining to non-elected inventions must be removed from the claim 51.

2. The drawings filed 1/5/06 has been entered and approved by the examiner.

3. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states reference must be made to the sequence by use of the assigned identifier, the identifier being SEQ ID NO. Sequences in Figure 1 must be identified by their corresponding SEQ ID NO:. Sequences in the specification must also be identified by SEQ ID NO:, e.g. page 18. Compliance with sequence rules is required.

Claim Rejection, 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 46-48 and 52-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

invention.

Claim 45 is indefinite because the hybridization conditions are not specified. The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claim cannot be determined without the disclosure of said conditions.

Claim 48 is indefinite because it is not clear when polynucleotide is about 300 base pairs as compared to about 300 base pairs.

Claims 46-48 and 52-53 are rejected for depending on an indefinite base claim and failing to resolve the issues raised above.

Claim Rejections - 35 USC 101 and 35 USC 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement

> thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-53 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A specific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known or immediately apparent, which can be implied by the specification alone, or taken in combination with the knowledge of one skilled in the art. A well established utility must also be specific and substantial as well as credible. Based on the record, there is not a "well established utility" for the claimed invention. The specification has asserted utilities for the specifically claimed invention of claims 41-53.

Applicant has added new claims 41-53 and argues support for the utility of the polynucleotide of the newly added claims can be found on page 71, line 36 to page 73, line 26. Applicant also argues since the polynucleotide was mapped

to chromosome 21q22.3, the polynucleotide of the present invention can be used to detect Down Syndrome trisomy or partial trisomy. Applicants' arguments have been fully considered but are not found persuasive. Even though polynucleotide can be mapped to chromosome 21q22.3 there is no nexus between detecting Down Syndrome trisomy or partial trisomy and use of claimed invention. As disclosed in the specification (page 73) many other polynucleotides map to chromosome 21q22.3, e.g. trefoil factor collagen IV, collagen VIII, interferon receptors and many other diseases are manifested due the association of genes to said chromosome, e.g. Knobloch syndrome, familial platlet disorder. Michaud (Michaud et al Genomics Vol. 68, pages 71-79, 2000) discloses to date 111 genes are known that map to chromosome 21, many only partially characterized (page 71). Michaud also discloses many unidentified genes for genetic disorders map to 21q22.3 (page 78). In fact the gene isolated by Michaud was is disclosed probably not triplicated in the partial trisomy 16 mouse model of Down Syndrome Ts65Dn (page 78). Gibson (Gibson et al, Clin. Genet. Vol. 59, pages 438-443, 2001) discloses currently considerable controversy exists as to whether any specific region(s) of chromosome 21 must be trisomic in order to produce the clinical features of Down Syndrome (page 438). The disease which shows linkage to the z219a polynucleotide of SEQ ID NO:1 is neither known nor disclosed. There is insufficient support in the specification or prior art for use of z219a polynucleotide to detect Down Syndrome trisomy or partial trisomy. Therefore based on the art it is very possible the z219a polynucleotide may be involved in an as yet, unknown disease state. Therefore

further experimentation is requited to determine the utility for z219a polynucleotide or fragments thereof.

The specification teaches a polynucleotide (SEQ ID NO:1) encoding the polypeptide of SEQ ID NO:2. The specification discloses the polypeptide of SEQ ID NO:2 is a novel polypeptide human 2-19 polypeptide homologue (Z219A) belonging to the family of cytokines. Z219A has some sequence similarity to murine EF-7 protein, human 2-19, human D87120 and z219a. The functionality of murine EF-7 protein, human 2-19, human D87120 and z219a is not disclosed. Z219A is also shown to expressed in a wide variety of tissues. Z219A is claimed to be useful as modulating agents in regulating a variety of cellular processes, useful for screening assays, detection assays, predictive assays and methods of treatment. However, no disclosure is provided within the instant specification on what specific function a putative Z129A protein possesses, or how to specifically assay for such; nor are any cell types/tissues disclosed that specifically express this protein; nor are any disease states disclosed that are directly related to Z129A dysfunction.

Accordingly, the instant specification provides insufficient guidance on how to use the disclosed Z129A proteins and therefore the nucleic acids of the instant invention, because no function for the Z129A protein is known, or disclosed. Likewise, expression vectors and host cells whose sole function is to make Z129A proteins lack utility for these same reasons. In order to practice the invention one of skill in the art would have to identify proteins and nucleic acids encoding said proteins having Z129A specific activity. However, the

specification does not provide a disclosure for identifying said activity. In particular, no assays are described in the specification by which one of ordinary skill in the art could extrapolate as to what constitutes functional characteristics of Z129A polypeptide, except for possessing a motifs 1-5. The significance of motifs 1-5 as it relates structure to function is not disclosed. Therefore, because it is unknown, nor disclosed, what specific ligand/agonist/ antagonist interacts or binds to Z129A, and because cytokines, by definition, possess their own unique biological activities/functions and ligands, it would be impossible for the skilled artisan to determine how to use Applicant's invention. It would require undue experimentation to first discover the function/activity of Z129A, as well as what unique ligands interact with Z129A. The divergent actions and specificity of the cytokine is described in the references (see previous office action) of Yoon et al, Structure, Vol. 13, pages 551-564, April 2005; Pestka et al, Immunological Reviews, Vol. 202, pages 8-32, 2001; Trinchieri, Immunological Reviews, Vol. 202, pages 5-7, 2001; Chang et al, Leukemia, Vol 17, pages 1263-1293, 2003; and Schein, Current Pharmaceutical Design, Vol. 10, No. 31, pages 3853-3855, 2004. The references show that cytokines are highly divergent in their structure and cellular functions. They require different receptors, have different activity. Structure does not necessarily predict function. For example, Yoon discloses two similar polypeptides vIL-10 and hIL-10 (83% identical) have different effects, i.e. in contrast to hIL-10, vIl-10 is unable to co stimulate thymocyte and mast cell proliferation and does not induce B cell MHC class II expression. Also vIL-10 exhibits a 1000 fold lower affinity for cell surface IL-10R1 than hIL-10 on human

cells (page 551, column 2. Peska discloses there are numerous cytokines which interact with numerous receptors and have divergent effects. Schein specifically states "We must know more about cytokines than what region of their surface mediates binding to a specific cell surface protein. Modern drug design demands that we identify the binding partners, cellular environment and even possible substrates of cytokines and growth factors", page 3854. In instant case the surface that mediates binding to a specific cell surface protein, binding partners, cellular environment and possible substrates of Z129A are not known. It is not even known which family of cytokines Z129A belongs.

Further, the specification does not teach which particular amino acids are critical for Z129A protein's function that are encoded by these polynucleotides. In other words, such structurally deficient polynucleotides containing random mutations would be expected by the skilled artisan to result in nucleic acid molecules encoding inactive proteins, even if such activity becomes known. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence. Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for Z129A function, if ever discovered, would prevent the skilled artisan from determining whether any modification or mutation to the single disclosed human Z129A DNA molecule could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within a Z129A protein itself would be predicted to adversely alter its biologically active 3-dimensional conformation,

without undue experimentation to determine otherwise; especially when no assays to distinguish such functional nucleic acid molecules are known or disclosed.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to the instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the protein of SEQ ID NO:2 or fragments thereof, useful to identify drugs that affect said protein and modulate its activity. Neither the specification nor the art of record disclose the nucleic acid of SEQ ID NO:1, or fragments thereof, useful to identify drugs that affect the protein encoded by said nucleic acid molecule and modulate its activity.

Similarly, neither the specification nor the art of record disclose any instances where disorders can be affected by interfering with the activity using the Z129A or fragments thereof. Thus the corresponding asserted utilities are essentially methods of using Z129A or fragments thereof to identify disease states associated with Z129A dysfunction and as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with Z129A polypeptide which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further

research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed Z129A and fragments thereof, further experimentation is necessary to attribute a utility to the claimed polynucleotides. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

The use of the nucleic acids as probes for identifying an individual from a biological sample, forensic identification and tissue identification using the Z129A nucleic acid/protein does not provide a specific and substantial asserted utility or a well established utility, and is discussed below. The basis for identifying an individual from a biological sample is by using restriction fragment length polymorphism and determining individual identification by allelic differences. For the claimed nucleic acid molecule to be used in the manner specified, it must be demonstrated that there is polymorphism present and the knowledge of the structural characteristics of the allelic variants, if they exist. Neither the specification nor the prior art discloses polymorphism (allelic variants) of instant invention. Therefore undue experimentation would be expected by the skilled artisan to isolate allelic variants of the protein of unknown function of instant invention result and use it in the manner suggested. Further, the specification,

nor prior art suggests any disease states where the Z129A protein of instant invention is involved. Tissue identification is a general utility applicable to all nucleic acids. All members of the cytokine family may be used for forensic identification, tissue identification, screening of candidate drugs. However, for a utility to be well-established it must be specific, substantial. However, the particulars of screening of candidate drugs, that target claimed Z129A, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:1 and fragments thereof. Because of this, such a utility is not specific and does not constitute a well-established utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed Z129A is only useful in the sense that the information that is gained from the assay is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the TNFRL family. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants individual Z129A is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this

consideration, the individually claimed method of using claimed Z129A has no well-established use. The artisan is required to perform further experimentation on the claimed Z129A itself in order to determine to what use any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the claimed Z129A and a disease or disorder. The presence of claimed Z129A in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed Z129A and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed Z129A to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed Z129A is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of claimed Z129A as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed Z129A and any disease or disorder and the lack of any correlation between the claimed Z129A with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on

the observation itself. Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, the cytokine family to which the polypeptide encoded by the polynucleotide of SEQ ID NO:1 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific and utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the cytokine family has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to

argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed Z129A, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by the ion channel family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, does not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide encoded by the claimed nucleic acid. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:2 and the polynucleotide of SEQ ID NO:1. The specification has not described the family of Z129A in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1 and variants and fragments thereof have any substantial use. The record shows that the family of proteins having cytokine domains is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

As disclosed in the rejection above, it is unknown, nor disclosed, what specific ligand/agonist/ antagonist interacts or binds to Z129A, and because cytokines, by definition, possess their own unique biological activities/functions

and ligands, it would be impossible to determine how to use Applicants invention, as described as claimed, without requiring undue experimentation to first discover the function/activity of Z129A, as well as what unique ligands interact with Z129A. The assays and antibodies suggested by applicant only provide tools for further experimentation on the protein and do not identify a specific use for the protein of instant invention.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed Z129A might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates".)

The prior rejection under 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed Z129A nucleic acid, vectors containing said nucleic acid have no utility, methods of its use are also lack of utility.

8. Claims 41-53 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed Z129A nucleic acid, variants thereof, vectors containing said nucleic acid further experimentation is necessary to attribute a utility to the claimed nucleic acid encoding Z129A polypeptides and variants thereof.

The claims fail to disclose how to use the claimed invention for the reasons given above (lack of utility). Further the claims are drawn to an orphan Z129A. The claimed nucleic acid encodes an orphan Z129A whose activity, activating ligands and functionality have not been disclosed. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed Z129A. There is no disclosure of the specific compounds that are transported, proteins activated in the signal transduction pathway or what ligand is capable of binding to the polypeptide encoded by the claimed polynucleotide, so as to disclose a specific function for the claimed polynucleotide. Therefore nucleic acids encoding unrelated and inactive proteins are encompassed by the claims. The specification does not disclose how to produce active variants or how to use inactive ones. Substitutions that result in active variants are not disclosed. Substitutions that are detrimental to Z129A variant activity are not disclosed. There is no disclosure of how to assay variants since the ligand and function of the claimed invention is unknown.

The complex nature of cytokines (disclosed above) and the unpredictability of assigning a function to Z129A with no known ligand, activity, or function is described in the rejection under 35 USC 101 and 35 USC 112, 1st paragraph.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

The activity of the Z129A is unknown. Polynucleotides that would hybridize to the polynucleotide of SEQ ID NO:1 encompass unrelated and inactive variants. Applicant has not disclosed how to use unrelated and inactive variants. Applicant has not disclosed how to isolate or make functional variants encompassing the limitations of the claimed invention. Instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds, which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The claimed compounds in instant application are isolated polynucleotides that hybridize to a particular polynucleotide. The critical feature of the invention as it relates structure to function is not required to be contained in the hybridizing sequence. In Ex parte Maizel the Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to

any nucleic acid isolated by the hybridization, given the lack of guidance regarding what sequences would hybridize specifically to the polynucleotide of SEQ ID NO:1 and sequence complementary thereto, and not hybridize to other, unrelated sequences. Further, many of the polypeptides encoded by the nucleic acids isolated will be unrelated to the protein of SEQ ID No:20, being devoid of its characteristic structural and functional features. The specification does not disclose how to use the unrelated compounds isolated by claimed method. Further, many compounds isolated may be inactive. The specification does not disclose how to use inactive compounds. Inactive compounds may be truncated polynucleotides devoid of function and lacking the critical feature that relates structure to function. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polynucleotides and polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins and nucleic acids (since mutations of SEQ ID NO:1 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

As is evidence in the discussions *supra*, undue experimentation would be required by the skilled artisan to make and use the instant invention.

6. Claims 41-53 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to polynucleotides which hybridize to the polynucleotide of SEQ ID NO:1, hybridize to the 21q22.3 region of human chromosome 21 or polynucleotides produced by the polymerase chain reaction when the oliginucleotide according to claim 49 is used in the polymerase chain reaction. The claims are also drawn to vector comprising said. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure that is required for functionality (biological activity. Thus, the claims are drawn to a genus of polynucleotides that is defined only by hybridization language.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular

portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all polynculeotides that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed nucleic acid sequences, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. The claims are not even directed to polynucleotides which encode a particular biological functional protein. Therefore nucleic acids encoding non-functional or functionally unrelated proteins to Z219A are encompassed by the claims. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional

protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specific activity of the protein of SEQ ID NO:2. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence or polynucleotides that hybridize with a particular polynucleotide sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature. Also, if one skilled in the art were to isolate a polynucleotide by hybridization he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a non-functional polypeptide. Nor would he be

able to say whether the isolated polypeptide was functionally related to the polynucleotide of SEQ ID NO:1.sequence existed in nature.

There are billions of sequences that could potentially fit the claimed genus. To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}). The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + L(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible

sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300-nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:2, is 235 amino acids long, and the reference nucleotide sequence, SEQ ID NO:1 is 876 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 80% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6×10^{23} and 1.6×10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active Z219A polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology with SEQ ID NO:2, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in case to case painstaking experimental study to determine active PRO1885 variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active Z219A with an amino acid sequence differing from SEQ ID NO:2 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:2, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:2 encoded by SEQ ID NO:1 which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing

date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:1 but not the full breadth of the claims meets the written description provision of 35 U.S.C.j112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

7.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 41-52 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 6388064. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both disclose the isolated polynucleotide of SEQ ID NO:1 and a complementary polynucleotide. Patent No. 6388064 and instant application also disclose a vector comprising the polynucleotide of SEQ ID NO:1. The polynucleotide of claim 1 of 6388064 would hybridize to the polynucleotide of SEQ ID NO:1. The claims are also not patentably distinct from each other because they both disclose a polynucleotide the polynucleotide of SEQ ID NO:1 and a molecule complementary thereto. The common feature of claim 41-52 of instant application and claims 1 and 4 of

Patent 6388064 is the polynucleotide of SEQ ID NO:1 and a molecule complementary thereto.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

1. Claims 41-45, 49-52 are rejected under 35 U.S.C. 102 (a) as being anticipated by NCI-CGAP (EST Database Accession number AA515600, 19 August 1997) and Hillier et al (EST Database Accession number AA402158, 16 May 1997)

NCI-CGAP discloses an oligonucleotide which ahs 100% query match and 100% best local similarity with SEQ ID NO:13. Hillier et al discloses an oligonucleotide which ahs 100% query match and 100% best local similarity with SEQ ID NO:14. Since the aforementioned oligonucleotides were clone they were inherently contained in a vector. The oligonucleotide disclosed by NCI-CGAP and Hillier et al would both hybridize to the polynucleotide of SEQ ID NO1, are contained in a vector, can be produced by a polymerase chain reaction and would hybridize to chromosome 21, thereby meeting the limitations of claims 41-45, 49-52.

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
April 3, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER